

Claims.

What is claimed is:

1. A method for inhibiting cell adhesion in a mammal which comprises administering to the mammal a pharmaceutical composition comprising a methimazole derivative or tautomeric cyclic thione or mixtures thereof in an amount effective for prevention, inhibition or suppression of cell adhesion.
2. A method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to the mammal a pharmaceutical composition comprising a methimazole derivative or tautomeric cyclic thione or mixtures thereof in an amount effective for prevention, inhibition or suppression of cell adhesion.
3. The method according to claim 1, wherein the disease or condition is one or more of acute lung injury, allergic rhinitis, Alzheimer's disease, arthritis, asthma, atherosclerosis, autoimmune glomerulonephritis, Behcet's disease, cancer, cerebral infarcts, chronic hepatitis, cirrhosis, cutaneous anaphylaxis reaction, cutaneous vasculitides, delayed type hypersensitivity reaction, diabetes, disseminated intravascular coagulation, eosinophilic granuloma of the lung, gastritis, giant cell arteritis, Graves' disease, haemorrhagic shock, hypertensive vascular disease, hypothyroidism, inflammatory bowel disease (Crohn's disease and ulcerative colitis), inflammatory dermatoses, intestinal infarcts, Kawasaki's disease (mucocutaneous lymph node syndrome), lymphoid interstitial pneumonia, malaria, meningitis, multiple sclerosis,

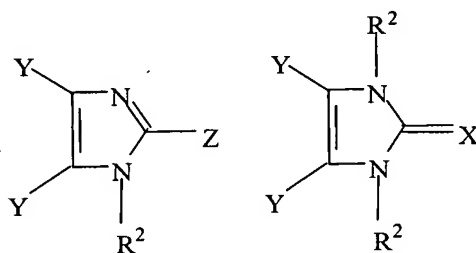
15 myocardial infarcts, organ transplantation (host vs. graft and graft vs. host),
polyarteritis nodosa, polymyositis/dermatomyositis, psoriasis, pulmonary
infarcts, renal infarcts, reperfusion injury following ischemia, Rickettsial
vasculitis, sarcoidosis, sepsis, sjogren's disease, stroke, systemic lupus
erythematosus, thermal injury (burns), thromboangiitis obliterans (Buerger's
disease), thrombosis, thyroiditis, tuberculosis, vasculitis, and Wegner's
granulomatosis.

4. A method of preventing, inhibiting or suppressing cell adhesion in a mammal comprising the step of administering to the mammal a pharmaceutical composition comprising a methimazole derivative or tautomeric cyclic thione or mixtures thereof in an amount effective for prevention, inhibition or
5 suppression of cell adhesion, wherein the cell adhesion is VCAM-1 mediated and a pharmaceutically acceptable carrier.
5. The method according to claim 4, wherein the cell adhesion is mediated by VCAM-1 and E-selectin.
6. The method according to claim 5, wherein the cell adhesion is IRF-1 dependent VCAM-1 mediated cell adhesion.

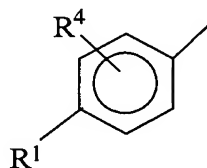
7. A method of preventing, inhibiting or suppressing cytokine-induced cell adhesion in a mammal comprising the step of administering to the mammal a pharmaceutical composition comprising a methimazole derivative or tautomeric cyclic thione or mixtures thereof in an amount effective for prevention, inhibition or suppression of cell adhesion, wherein the cell adhesion is VCAM-1 mediated and a pharmaceutically acceptable carrier.
8. The method according to claim 7, wherein the cell adhesion is mediated by VCAM-1 and E-selectin.
9. The method according to claim 8, wherein the cell adhesion is IRF-1 dependent VCAM-1 mediated cell adhesion.
10. The method according to claim 7, wherein the cytokine is TNF-alpha.
11. The method according to claims 1, 4 or 7, wherein the method is used for preventing, inhibiting or suppressing cell adhesion-associated inflammation.
12. The method according to claim 7 wherein the method is used for preventing, inhibiting or suppressing cytokine-induced cell adhesion-associated inflammation.
13. The method according to claims 1, 4 or 7, wherein the method is used for preventing, inhibiting or suppressing cell adhesion associated with immune or autoimmune responses.
14. The method according to claim 4, wherein the method is used to treat or prevent a disease selected from the group consisting of wherein the disease or condition is one or more of adult respiratory distress syndrome, AIDS, allergy conditions, arteriosclerosis, arthritis, asthma, atherosclerosis, cardiovascular diseases, detaching retina, harmful platelet aggregation, inflammation,

inflammatory bowel diseases, multiple sclerosis, neoplastic diseases, ophthalmic inflammatory conditions, osteoarthritis, osteoporosis, psoriasis, regional enteritis, rejection after transplantation, reocclusion following thrombolysis, reperfusion injury, Sjogren's Syndrome, skin inflammatory diseases, systemic lupus erythematosus, thrombosis, Type I diabetes, thyroiditis and wounds.

15. The method according to claim 1, 4 or 7, wherein the pharmaceutical composition comprises a safe and effective amount of an active compound selected from:



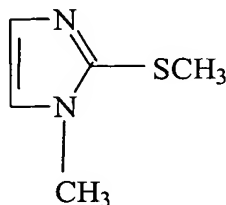
wherein Y is selected from the group consisting of H, C₁-C₄ alkyl, C₁-C₄ substituted alkyl, -NO₂, and the phenyl moiety:



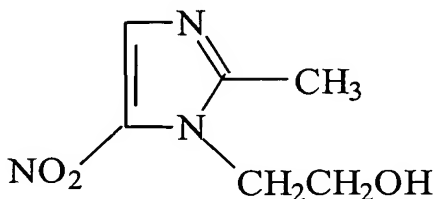
- 15 and wherein no more than one Y group in said active compound may be the phenyl moiety; R¹ is selected from the group consisting of H, -OH, C₁-C₄ alkyl, and C₁-C₄ substituted alkyl; R² is selected from the group consisting of H, C₁-C₄ alkyl and C₁-C₄ substituted alkyl; R³ is selected from the group

consisting of H, C₁-C₄ alkyl, C₁-C₄ substituted alkyl, and -CH₂Ph; R⁴ is selected from the group consisting of H, C₁-C₄ alkyl, and C₁-C₄ substituted alkyl; X is selected from S and O; and Z is selected from -SR³, -OR³ and C₁-C₄ alkyl; and wherein at least two of the R² and R³ groups in said compound are C₁-C₄ alkyl when Y is not a phenyl moiety, and at least one Y is -NO₂ when Z is alkyl; and a pharmaceutically-acceptable carrier.

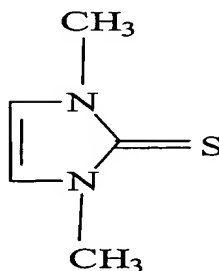
16. The method according to claim 15, wherein Z is selected from --SR³ and OR³.
17. The method according to claim 16, wherein Z is --SR³ and X is S.
18. The method according to claim 17, wherein Y is H.
19. The method according to claim 18, wherein R³ is C₁ -C₄ alkyl.
20. The method according to claim 19, wherein R³ is methyl.
21. The method according to claim 20, wherein at least one of the R² groups is methyl.
22. The method according to claim 20, wherein both R² groups are methyl.
23. The method according to claim 15, wherein the active compound has the formula



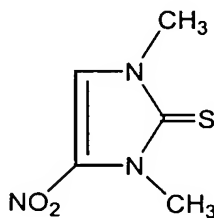
24. The method according to claim 15, wherein the active compound has the formula



25. The method according to claim 15, wherein the active compound has the formula:

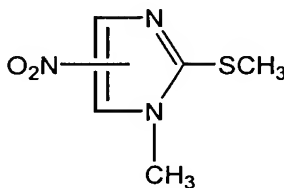


26. The method according to claim 15, wherein the active compound has the



formula:

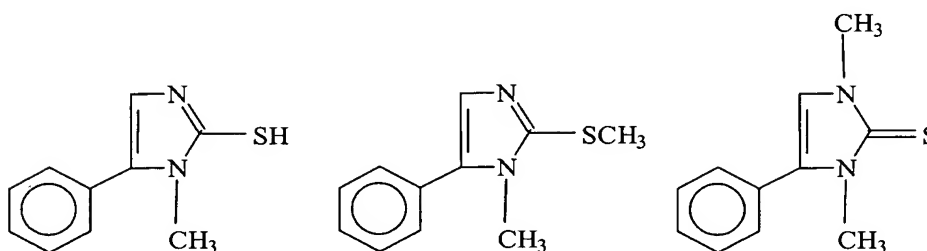
27. The method according to claim 15, wherein the active compound has the formula:



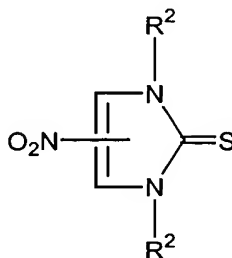
28. The method according to claim 17, wherein one of the Y groups is the phenyl moiety.

29. The method according to claim 26, wherein R¹ and R⁴ are H.

30. The method according to claim 27, wherein R^3 is methyl and at least one of the R^2 groups is methyl.
31. The method according to claim 28, wherein R^3 is H.
32. The method according to claim 29, wherein both R^2 groups are methyl.
33. The method according to claim 15, wherein the active compound is selected from the group consisting of:



34. The method according to claim 15, wherein the pharmaceutical composition is in prodrug form.
35. The method according to claim 15, wherein the pharmaceutical composition comprises from about 0.01% to about 25% of the active compound and from about 75% to about 99.99% of the pharmaceutically-acceptable carrier.
36. The method according to claim 1, 4 or 7, wherein the pharmaceutical composition comprises a safe and effective amount of an active compound having the formula:

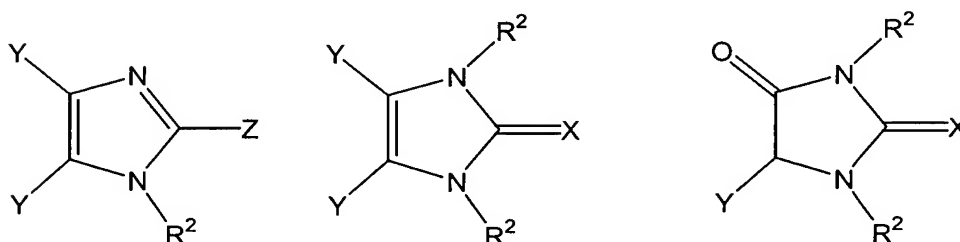


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wherein R^2 is selected from the group consisting of H, C_1 - C_4 alkyl and C_1 - C_4 substituted alkyl.

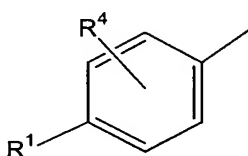
37. The method according to claim 34, wherein the R^2 is selected from the group consisting of C_1 - C_4 alkyl and C_1 - C_4 substituted alkyl.
38. The method according to claim 35, wherein the R^2 is methyl.
39. The method according to claim 1, 4 or 7, wherein the pharmaceutical composition comprises a safe and effective amount of a compound selected from

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wherein Y is selected from the group consisting of H, C_1 - C_4 alkyl, C_1 - C_4 substituted alkyl, $-NO_2$, and the phenyl moiety

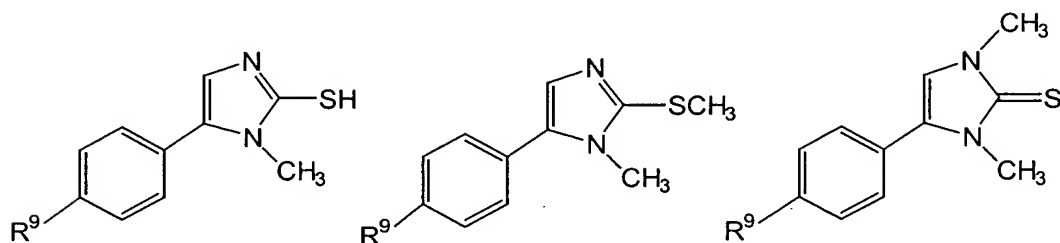
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and wherein no more than one Y group in said active compound may be the phenyl moiety; R^1 is selected from the group consisting of H, $-OH$, halogens, C_1 - C_4 alkyl, C_1 - C_4 substituted alkyl, C_1 - C_4 ester and C_1 - C_4 substituted ester; R^2 is

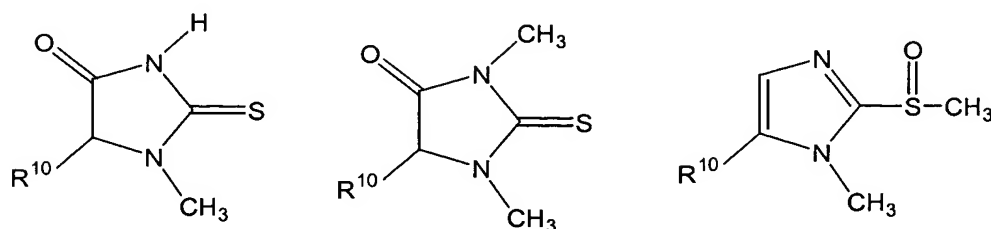
- 15 selected from the group consisting of H, C₁-C₄ alkyl and C₁-C₄ substituted alkyl; R³ is selected from the group consisting of H, C₁-C₄ alkyl, C₁-C₄ substituted alkyl, and -CH₂Ph; R⁴ is selected from the group consisting of H, C₁-C₄ alkyl and C₁-C₄ substituted alkyl; X is selected from S and O; Z is selected from -SR³, -OR³, -S(O)R³, -SR³, and C₁-C₄ alkyl; and wherein at least two of the R² and R³ groups in said compound are C₁-C₄ alkyl when Y is not a phenyl moiety, and at least one Y is -NO₂, when Z is alkyl: and a pharmaceutically-acceptable carrier.
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40. The method according to claim 37, wherein the active compound is selected from the group consisting of



- 5 wherein R⁹ is selected from the group consisting of -OH, -M and -OOCCH₂M; wherein M is selected from F, Cl, Br and I.

41. The method according to claim 38, wherein the active compound is selected from the group consisting of



- wherein R¹⁰ is selected from the group consisting of H, -NO₂, Ph, 4-HOPh and 4-MPh, wherein M is selected from F, Cl, Br and I.

42. A method of treating a condition involving vascular adhesion of leukocytes, comprising: (a) identifying a subject suspected of having a condition involving aberrant leukocyte adhesion to vascular endothelium; and (b) administering to the subject an amount of a pharmaceutical composition comprising a
- 5 methimazole derivative or tautomeric cyclic thione or mixtures thereof sufficient to decrease cell surface expression of at least one of VCAM-I and E-selectin on endothelial cells, thereby reducing adhesion of leukocyte cells to vascular endothelium.
43. The method according to claim 40, wherein one or more additional active ingredients are combined with the composition of the present invention, either administered separately or in the same pharmaceutical composition, selected from the group comprising (a) VCAM-1 antagonists; (b) steroids; (c)
- 5 immunosuppressants; (d) antihistamines; (e) non-steroidal anti-asthmatics; (f) non-steroidal antiinflammatory agents (NSAIDs); (g) cyclooxygenase-2 (COX-2) inhibitors; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) antagonists of the chemokine receptors; (j) cholesterol lowering agents; (k) anti-diabetic agents; (l) preparations of interferon beta; (m) anticholinergic
- 10 agents; and (n) antibiotics.

44. A method of screening for compounds capable of preventing, inhibiting or suppressing VCAM-1 mediated cell adhesion or preventing, inhibiting or suppressing cell adhesion-associated inflammation in a mammal, comprising:
- (a) contacting the mammal with a test compound;
 - 5 (b) measuring an effect of the test compound on leukocyte adhesion or migration or both; and
 - (c) determining whether the test compound is an inhibitor of the adhesion or migration activities or both of the leukocytes.
45. The method according to claim 42, wherein the measuring an effect of the test compound comprises one or more of measuring IRF-1 RNA expression levels; measuring IRF-1 protein expression levels; measuring IRF-1 dependent VCAM-1 promoter activation; measuring cytokine -increased IRF-1 RNA
- 5 expression levels; measuring cytokine -increased IRF-1 protein expression levels; measuring cytokine-increased IRF-1 dependent VCAM-1 promoter activation; measuring TNF-alpha-increased IRF-1 RNA expression levels; measuring TNF-alpha-increased IRF-1 protein expression levels; and measuring TNF-alpha-increased IRF-1 dependent VCAM-1 promoter
- 10 activation.
46. The method according to claim 42, wherein the measuring an effect of the test compound comprises one or more of measuring VCAM-1 RNA expression levels; measuring cytokine-increased VCAM-1 protein expression levels; measuring cytokine-increased VCAM-1 promoter activation measuring TNF-

- 5 alpha-increased VCAM-1 RNA expression levels; measuring TNF-alpha increased VCAM-1 protein expression levels; and measuring TNF-alpha increased VCAM-1 promoter activation.

47. A method of screening for compounds capable of cell adhesion inhibitory activity in VCAM-1 expressing cells, comprising:
- (a) contacting VCAM-1-expressing cells with a test compound;
 - (b) contacting the VCAM-1-expressing cells to VCAM-1 ligand
5 expressing cells;
 - (c) measuring an effect of the test compound on binding of the VCAM-1-expressing cells to VCAM-1 ligand expressing cells; and
 - (d) determining whether the test compound is an inhibitor of the
10 binding activities of the VCAM-1-expressing cells to VCAM-1 ligand expressing cells.
48. The method according to claim 45, comprising the further step prior to, concurrently with or subsequently to addition of the test compound, of contacting VCAM-1-expressing cells with a cytokine capable of inducing expression of VCAM-1.
49. The method according to claim 46, wherein the cytokine is TNF-alpha.
50. The method according to claim 47, wherein the VCAM-1-expressing cells are selected from the group comprising nonimmune target tissue cells, endothelial cells, and epithelial cells.
51. The method according to claim 47, wherein the VCAM-1-expressing cells are human aorta endothelial cells (HAEC).
52. The method according to claim 47, wherein the VCAM-1 ligand expressing cells are leukocytes.

53. The method according to claim 47, wherein the cells are allowed to remain in contact for at least 30 minutes.